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RESEARCH ARTICLE

Growth Hormone and Visual Stimulation Restore Normal Vision in Children with Cerebral Palsy

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ABSTRACT

A common problem in children affected by cerebral palsy, independently of its etiology, is the existence of visual impairment. In this retrospective study we analyzed the effects of Growth hormone (GH) administration (0,04 mg/kg/day, 5 days/week) together with visual stimulation with a tachistoscope in 42 children with cerebral palsy (22 boys, 20 girls, aged 2,48 ± 1,5 years [mean ± SD) in whom there was an evident lesion of the visual pathway. In 17 of these cases, prematurity was the responsible factor, while in the other 25 children, ischemic encephalopathy due to pre/perinatal problems was the origin of visual impairment. In addition, we analyzed three other children (1, 2 months and 1 year of age) in whom multicystic encephalopathy (due to severe hypoxia-ischemia at delivery) mainly affecting the occipital lobes was the responsible factor. Visual evoked potentials were recorded before beginning and after treatment, assessing the latency in ms of the N75, P100 and N140 waves, as well as the amplitude of the waves (μV). Treatment duration (mean ± SD) was 5.20 + 2.05 months. Completion of treatment was established by clinical criteria. The statistical significance of the data was carried out using the Wilcoxon test.

The treatment induced a significant decrease in the latency of N75, P100 and N140 ($p < 0.001$), as well as a clear tendency to increase the amplitude of the waves ($p < 0.05$). Of special interest is the case of a child affected by Multicystic Encephalopathy in which the cystic cavities in the occipital lobes detected by MRI before starting treatment (15 days of age) completely disappeared in a new MRI performed 1 year later. That child is now totally independent for activities of daily living. GH treatment did not produce any adverse effects. In summary, from our results we can conclude that the administration of GH added to visual stimulation with a tachistoscope is an effective and safe method for the repair of visual deficiencies in children with cerebral palsy, regardless of the existence or not of GH deficiency.

Keywords. - Cerebral palsy, Visual impairment, GH, tachistoscope, Myelination.

Introduction

Cerebral palsy (CP) is the most common cause of physical disability in childhood.[1] The estimated mean prevalence of CP in the general population is 2/1000.[2] CP is defined as a persistent but not progressive disorder of posture and movement system, associated with functional activity limitations and sensorial, cognitive, communications problems, epilepsy, and musculoskeletal system problems.[2] Although classically CP has been characterized by the existence of motor disabilities, many of these CP children display a number of cognitive and sensorial affectations; among these, mental disadvantage is the most frequent one (IQ < 50), followed by active seizures, and other functional affectations such as impaired vision and even blindness; in addition, up to 80% of CP children have at least some impairment of speech, and half of these CP children have gastrointestinal and feeding problems.[3]

The main causes of CP include abnormal intrauterine developments, due to maternal-fetal infections, asphyxia before birth, hypoxia during childbirth, head trauma during labor and delivery, as well as complications in the prenatal period (massive hemorrhage by Vasa previa) and perinatal period. Apart from these, prematurity is responsible for 40-50% of CP cases.

Periventricular Leukomalacia (PVL) and parenchymal venous infarction involving the germinal matrix/intraventricular hemorrhage have long been recognized as the two most important white matter disorders responsible for most cases of cerebral palsy in surviving preterm infants. However, more recent studies using magnetic resonance imaging to assess the preterm brain have documented two new situations, adding to the spectrum of white matter affectation that occurs in prematurity: punctate white matter lesions and excessively high diffuse signal strength. These appear to be more common than PVL but less significant in terms of their impact on individual neurodevelopment. However, they may be associated with later cognitive and behavioral disorders known to be common after preterm birth.[4]

A recent and interesting hypothesis suggest that chronic fetal hypoxemia (CHX) may cause fetal brain injury by upregulating inflammatory cytokine cascades, culminating in apoptosis pathway activation, increasing the lactate/pyruvate and decreasing the glutathione (GSH)/oxidized glutathione (GSSH) ratios, confirming a shift to a prooxidant state. The end result is a >30% decrease in hippocampal neuron density. CHX would trigger fetal brain inflammation inversely proportional to its severity characterized by increased apoptosis and neuronal loss. The authors suggest that CHX fetal brain injury is not directly caused by oxygen deprivation but rather would be an adaptive response that becomes maladaptive.[5]

Regardless of the causal factors responsible for the development of CP, the disease has a strong socioeconomic impact. Therapeutic approaches, such as physical therapy, occupational therapy, speech therapy, medications to control seizures, surgery to correct anatomical abnormalities, etc., have only a small benefit for those affected children.

The objective of this study is not to analyze the multiple therapeutic options and their results already described for the treatment of CP, but rather to focus on how a special situation such as impaired vision or blindness that is usually observed in these children can be treated. Since a large proportion of the brain serves visual function, cerebral palsy is a common cause of chronic cortical visual impairment in children,[6-12] for which no solution has been provided until now.

Several studies from our group have shown the fundamental role that Growth Hormone (GH) plays in brain function, even helping to recover, along with rehabilitation, many different brain injuries, including CP.[13-22] This is the reason why since 2010 we have been treating several children with CP and visual impairment with GH and specific visual stimulation. In this study we will retrospectively analyze the results obtained with this type of treatment. That is, this is not a clinical trial but a retrospective observational study of the results obtained with a specific stimulation used in CP children with visual impairment.

Methods

Among the children admitted to the Medical Center Foltra, between 2010 and 2021, for rehabilitation of the motor and cognitive sequelae produced by cerebral palsy, we detected that 42 of them presented an evident affectation of the visual pathway. Of these, 22 were boys and 20 girls, with a mean age of 2.48 ± 1.5 years (Mean ± Standard deviation [SD]). All of them had a clear diagnosis of cerebral palsy, and apart from the classic motor and sensory manifestations of this disease, there was a clear lesion of the visual pathway characterized by critical vision impairment and marked pallor of the optic nerve.

Children under one year of age went directly to our Center to be treated for their PC, while the rest, coming from very different places in Spain and Portugal, had been treated through rehabilitation, without success, in other Centers in their cities of origin.

Studies and treatments were conducted according to our protocols and in compliance with the Spanish legislation for using GH "off label" and the Code of Ethics of the World Medical Association (Declaration of Helsinki). Signed informed consent for using GH was obtained from the legal representatives of each patient.

Routine blood analysis, including plasma values of thyroid hormones and Insulin Growth Hormone Factor-I (IGF-I) were performed before commencing the treatment and at 3-months intervals later. Given the pathology and the age of the patient, we did not perform any provocative tests for analyzing pituitary GH secretion, despite the low height and low plasma IGF-I values.

In children in whom visual impairment had been detected, visual evoked potentials (VEPs) were recorded before starting treatment and after finishing it. The rationale for stopping visual stimulation and GH treatment was based on clinical observations (eg, visual interaction with the environment, looking at objects or relatives, grasping objects with hands...).

VEPs were recorded under stimulation with flashes of white light (XLTEC™ photic stimulator, Model XLPS-1F). Surface electrodes were used to record the electrical conduction of visual stimuli: Ag-AgCl; Oz FPZ, 10-20 system, with the active electrode in the occipital area (Oz), the impedance was always below 5 kohms. The mean of 100 curves was processed to analyze the final result of electrical transmission from the retina to the occipital lobes (Schwarzer EMG/EP topas 2). Latencies and amplitudes were analyzed.

In one of the patients, born in cardiac arrest due to a massive prenatal hemorrhage caused by a Vasa Previa, a brain Magnetic Resonance Imaging (MRI) was performed at 15 days of life and 1 year after finishing treatment.

In addition to specific motor and cognitive rehabilitation therapies for each case, in children with visual impairment the treatment used to induce visual recovery consisted of daily subcutaneous administration of GH (0.04 mg/kg/day, 5 days per week; Genotonorm, Pfizer, Spain), in the morning, followed by visual stimulation with a tachistoscope (repetitive white light flashes, 100-150 ms, carried out in 10 phases lasting 1 min each one, 80 flashes/min; 5 days/week; XLTEC™ photic stimulator, Model XLPS -1F). Stimulation was performed in a dark isolated room.

That is, each tachistoscope treatment session consisted of 10 phases and each stimulation phase consisted of 10 series of stimulation in which flashes of white light are released for 1 second at a frequency of 6-8 Hz. Between each series of stimulation there was a 5 second pause. Each stimulation phase produced between 60-80 flashes per minute. After each stimulation phase, a pause of 2 min was applied in absolute darkness. The face of the patient (maintained by a therapist) was placed at 20 cm from the tachistoscope. Figure 1 shows the tachistoscope used.

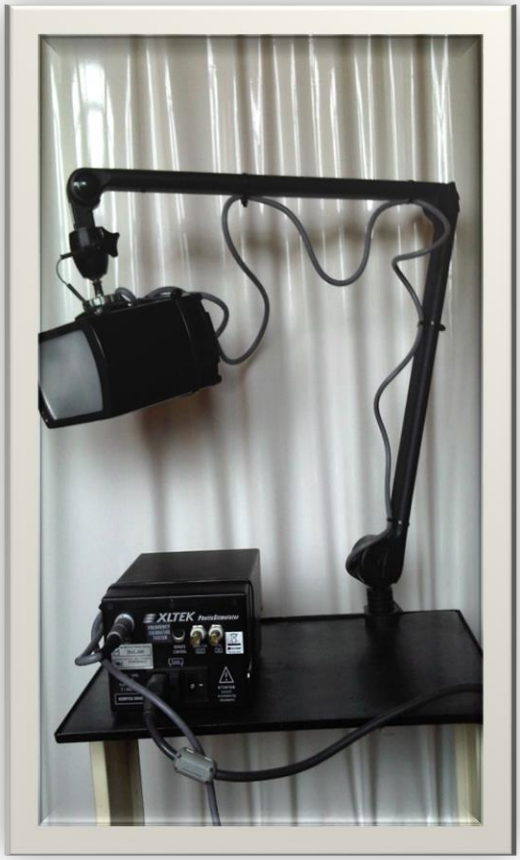

Figure 1.- Tachistoscope used for visual stimulation.

As described above, in one of the patients, born in cardiac arrest due to a massive prenatal hemorrhage caused by a Vasa Previa, a brain MRI was performed at 15 days of life and 1 year after finishing treatment.

Wilcoxon's rank sum test established statistical significance between pre-treatment and post-treatment VEP waveforms. $p < 0,05$ was considered to be significant.

Results

Cerebral palsy occurred due to prematurity (17 cases) that led to the development of periventricular leukomalacia, while in another 25 cases the cause was pre/perinatal hypoxia/ischemia. They developed ischemic encephalopathy. These are shown in Table 1.

Table 1.- Age and sex of children studied and months of treatment in each of them. F: Female. M: Male.

Patient Number	Age (years)	Sex	Months of treatment
1	1	F	2.5
2	1	M	3
3	2	F	3
4	2	F	7
5	0.25	M	2.5
6	2.25	M	5
7	3	M	3
8	3	F	3
9	2	F	3
10	6	F	8
11	4	F	8
12	0.8	M	7.5
13	2	F	6
14	0.5	M	3
15	2	F	12
16	3	M	6
17	0.2	M	3
18	1.5	M	5
19	2	F	3
20	3	M	5
21	3.5	F	6
22	4	M	8
23	2.25	F	5
24	1.8	M	3
25	3.5	M	6
26	2	M	4
27	4.5	F	8
28	1.5	M	6
29	1	F	4
30	2.6	M	5
31	1	M	3
32	1.5	F	4
33	3	F	6
34	3	M	7
35	2	F	5
36	2.5	M	5
37	2	F	4
38	1.5	F	3
39	4	M	7
40	2	F	8
41	1.5	M	4
42	2	M	6

Treatments lasted 5,20 + 2,05 months (Mean + SD).

Three other cases (aged 1, 3 months and 1 year) a multicystic encephalopathy developed that mainly affected the occipital lobes. These 3 children were not included in the study for statistical analysis, but the results obtained after treatment are also shown.

The evolution of VEPs in each patient is shown in Table 2. In this Table, latencies of the main waves (N75, P100 and N140) is indicated in milliseconds (ms), as well as the Amplitude registered pre- and post-treatment micro volts (μV).

Table 2.- Latency and Amplitude of each wave before commencing the treatment (pre) and after finishing it (post).

Patient	N75pre	N75post	P100pre	P100post	N140pre	N140post	Amp pre	Amp post
1	77,5	77	127	115	214	137	4,5	4,1
2	124	99	200	187	227	219	3,8	5,25
3	106	79	149	111	188	147	4,5	5,75
4	83	79	149	126	198	152	17,25	15,85
5	83	79	149	122	198	140	5,4	9,5
6	128	83	134	100	164	158	0,2	0,6
7	84	71	122	104	148	122	3,7	5,2
8	126	103	172	145	185	187	4,9	6,7
9	83	75	146	120	157	134	3,55	4,45
10	100	96	112	110	166	151	1,2	2,35
11	94	77	128	101	149	142	0,5	3,35
12	107	97	202	109	251	163	3,45	1
13	107	95	202	120	211	180	1	7
14	85	68	176	93	196	134	4,45	12,35
15	109	84	115	109	169	152	0,7	3,15
16	85	85	120	121	142	141	7,5	4,4
17	98	78	149	135	169	162	4,7	5,2
18	110	85	165	112	156	147	3,5	4,6
19	87	78	134	104	152	143	2,8	4,3
20	92	81	167	127	198	153	1,1	3,2
21	105	84	173	137	210	168	0,8	2,1
22	92	79	147	112	181	165	2,2	3,8
23	96	78	158	120	186	149	1,8	3,6
24	78	76	124	104	158	141	3,6	7,2
25	100	79	143	104	194	158	2,6	4,8
26	98	79	125	106	176	152	1,7	3,2
27	102	81	187	122	210	169	0,4	2,1
28	115	77	192	121	225	166	0,2	4,3
29	82	75	114	102	159	144	2,5	5,2
30	104	79	166	148	187	145	1,4	3,6
31	97	78	152	103	177	142	1,1	4,5
32	86	76	123	101	162	144	2,1	5,2
33	112	79	158	108	196	154	1,3	3,2
34	116	82	164	111	198	151	0,8	2,5
35	93	77	134	104	163	142	2,1	4,3
36	98	77	127	102	168	144	1,7	3,8
37	81	75	110	103	156	142	3,5	7,6
38	79	75	107	100	151	140	4,2	8,5
39	116	78	168	114	195	152	0,5	1,6
40	121	79	172	122	201	168	0,3	1,7
41	85	76	114	100	164	142	2,4	5,3
42	97	78	122	104	161	145	1,7	3,2

The results obtained were (Mean + SD): N75pre: 98,1+14,06; N75post: 80,61+7,31; P100pre: 147,57+27,04; P100post: 114,73+16,9; N140pre: 181,33+25,04; N140post: 152,07+16,52. The representation and statistical significance of these data is shown in Figure 2. As this Figure indicates the treatment induced a significant decrease in the latency of VEPs. The amplitude of the waves experienced a clear trend to increase at the end of the treatment $p < 0.05$),

Data obtained after the treatment period (Table 2) showed that latencies of the waves had been significantly reduced (Figure 2), while small significant changes were observed in amplitudes (Table 2).

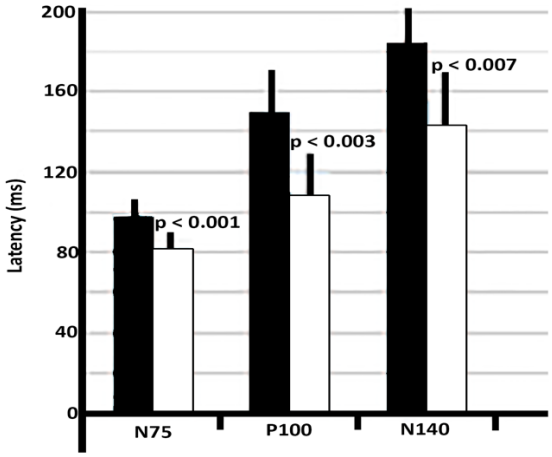

Figure 2.- Mean + SD of the EVPs registered in the group of children treated. Black rectangles: VEPs before commencing the treatment; White rectangles: VEPs after finishing the treatment.

The clinical evaluation of the patients indicated that the results obtained with the combination of GH administration and Visual Stimulation agreed with the clinical improvements in visual abilities.

Figure 3 shows an example of the evolution pre- and post-treatment of a child affected by Periventricular Leukomalacia, while Figure 4 shows the evolution of a patient with Multicystic Encephalopathy.

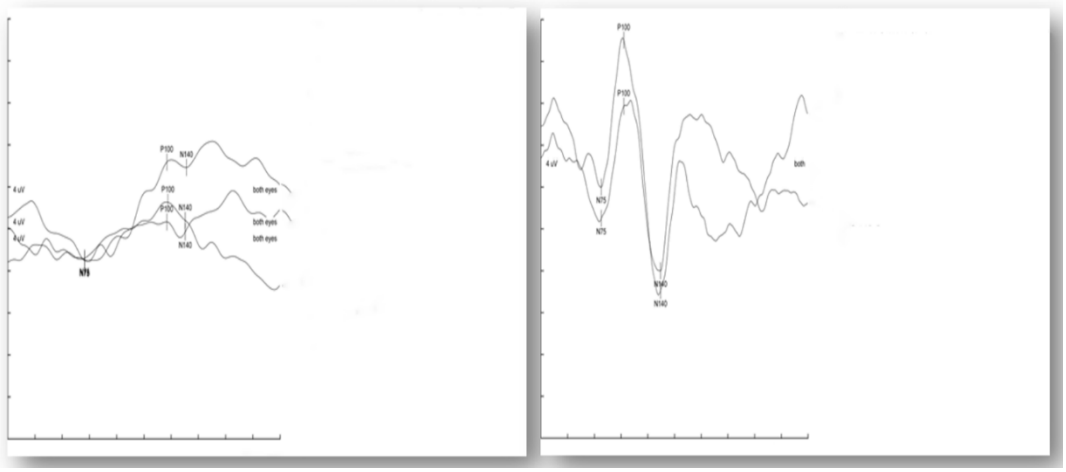

Figure 3.- VEPs recorded (both eyes) in a child affected by Periventricular Leukomalacia before (left) and after (right) finishing the treatment.

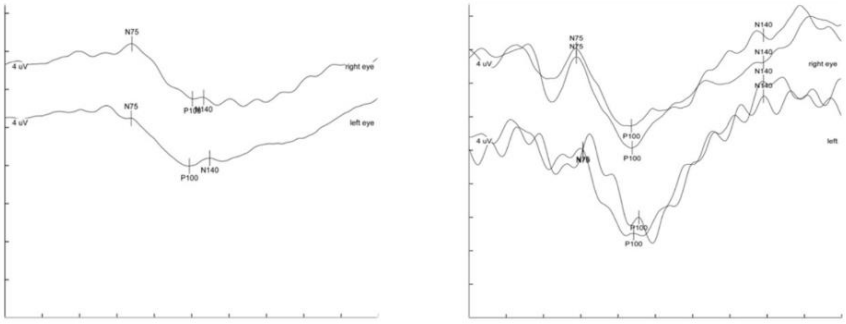

Figure 4.- VEPs recorded (both eyes) in a child affected by Multicystic Encephalopathy. before (left) and after (right) finishing the treatment. Note that after finishing the treatment two registers of VEPs were performed without differences between them.

Of special interest is the case of a child affected by Multicystic Encephalopathy produced by a Vasa Previa 15 days before the estimated date of birth. At home his mother started bleeding and thought she was in labor. When she arrived to the Hospital medical doctors said that it was a massive fetal hemorrhage. An emergency cesarean section was performed and the baby was born without vital signs and with cardiac arrest for the 15 minutes that he had been bleeding. Despite the resuscitation maneuvers, the electroencephalogram (EEG) carried out indicated that there was brain death (Figure 5). However, at the parents' request, life support was maintained for 15 days.

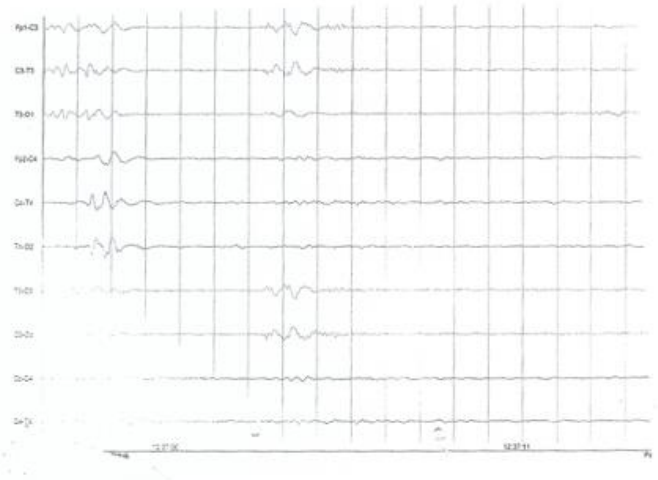

Figure 5.- EEG performed some hours after birth. Note that it is isoelectric without brain waves.

Ten days later VEPS were analyzed (Figure 6), but the record was isoelectric, without any transmission of the visual signal.

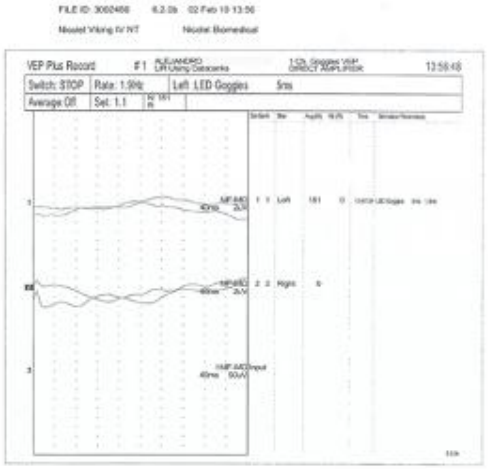

Figure 6.- VEPs recorded in both eyes. Note the absence of any wave.

On day 15, with the objective of taking a final decission a brain MRI was performed. The study indicated the existence of cerebral atrophy and multiple cystic cavities, specially important in the occipital lobes (Figure 7 upper). The prognosis was that if he lived he would be blind, deaf, dumb and he will suffer from spastic quadriplegia, and the parents were asked to wean the child from life support. However, the parents called us and brought the child to our Medical Center where we started the treatment at 17 days of life.

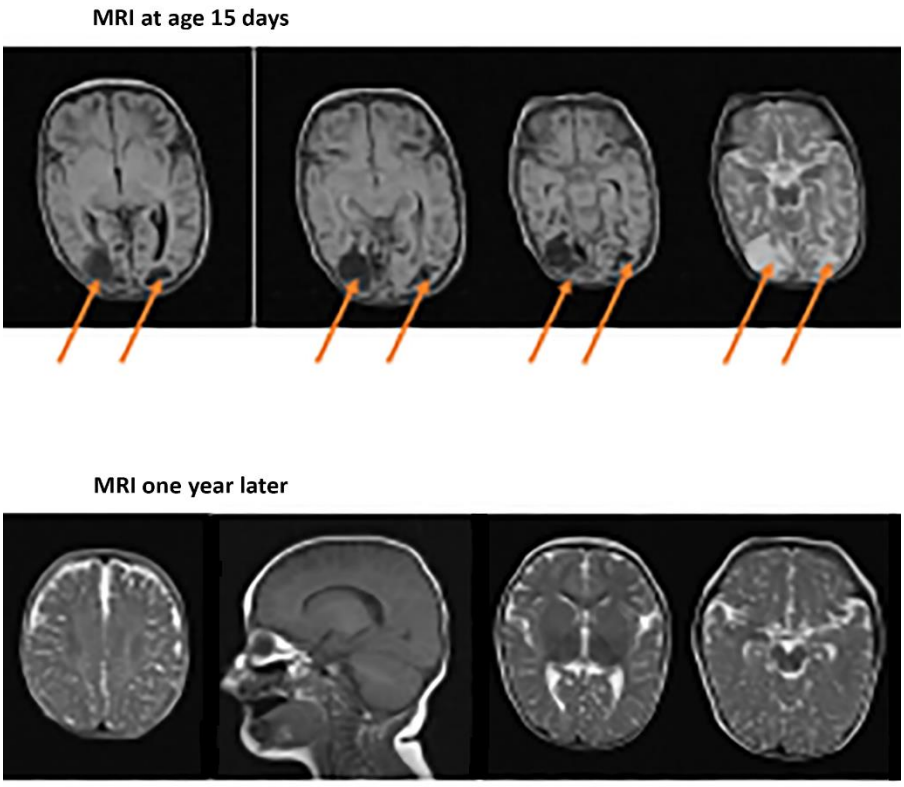

Figure 7.- MRi performed at 15 days of age (upper) and one year later (down). Red arrows (upper image) show the existence of important cystic cavities in both occipital lobes. One year later (down) a new MRi showed that the brain had been fully regenerated.

The child soon began to respond to the treatment administered and he recovered full normality at all levels. Currently, he is 12 years old, plays football, swims, study with normality and there is not any problem.
Figure 8 shows the child at 10 months of age.

Figure 8.- The child at 10 months of age. Note that his eyes are focused on the therapist, looking at her. Note also the perfect cephalic control and the absence of spastic quadriplegia.

In the other two cases of Multicystic Encephalopathy, who began treatment later, one of them recovered visual normality 7 months after starting treatment, while the other, older, who began treatment at 3 years of age VEPs continued to be delayed and they were still impaired 8 months after starting treatment, although a certain degree of visual perception did appear.

Discussion

As the Table 2 indicates, most of the patients presented an important delay in the appearance of the first wave (N75) after visual stimulation, and only in one case this latency was similar to the normal value (75 ms). More marked delays were observed when the second wave (P100) was registered. This wave had to appear at 100 ms, but its appearance was consistently delayed in all patients. Even more clear delays were observed in the latency of N140 wave. While its normal presentation occurs 140 ms after visual stimulation, it was consistently delayed in all the cases. Amplitudes before commencing the treatment showed a wide range of dispersion between patients.

From our results it seems to be clear that the combined treatment involving growth hormone administration and visual stimulation with white light flashes leads to a recovery of affected visual pathway in children with cerebral palsy.

Our study lacked a control group and this could lead to misinterpret the results obtained, but the study was carried out in children attending to the Medical Center Foltra only for rehabilitation and not for a clinical trial. This could be carried out by comparing the results obtained with the tachistoscope or GH, utilized alone, with the results of the combined stimulation, or comparing these results with those obtained with the administration of placebo, but we have to remark that this study is only a retrospective study. On the other hand, most of these children had been receiving intense stimulation in other centers previously, although not visual stimulation, without achieving significant results. Therefore, each child in our study may have been considered as his/her own control.

Electrophysiological evaluation of the visual pathway, using visual potential techniques, is a useful clinical tool for localization of dysfunction in a patient with visual loss.

Studies of vision using electrophysiological techniques are tests which record functional alterations in very early phases of a disease. Visual evoked potentials caused by sensory stimulation of a child's visual field are observed using electroencephalography.

Evoked potential amplitudes tend to be low, ranging from less than 1 μV to several μV, compared to tens of μV for EEG, millivolts (mV) for Electromyogram (EMG), and often close to 1 volt for Electrocardiogram (ECG).

VEPs are visually evoked electrophysiological signals extracted from the electroencephalographic activity in the visual cortex recorded from the overlying scalp. As visual cortex is activated primarily by the central visual field, VEPs depend on functional integrity of central vision at any level of the visual pathway including the eye, retina, the optic nerve, optic radiations, and occipital cortex.[23]

There is some recent evidence that a progressive excitation of adjacent cortical columns accounts for some Evoked Potentials (EP) components, indicating that the EP source is not from a single neurological structure but that it is the response of a larger section of the cortex to a specific afferent input.[24] In other words, the same neural structures that produce the spontaneous EEG activity may also be responsible for the generation of EP activity.[24]

The children we studied presented severe visual deficiencies, characterized by a delayed conduction from the retina to the occipital cortex, as VEPs showed. Most likely this means a deficient myelination that was improved with the treatment we used. Delayed myelination may be a finding unrelated to any specific pathology, only related to a delayed maturation of the central nervous system, but it is unlikely that this was the reason for the delayed latencies in the VEPs waves we observed, since these children suffered brain injuries produced by prematurity. Prematurity usually produces brain bleedings soon after birth dues to immaturity. The common manifestation of this affectation is Periventricular Leukomalacia, in which cerebral white matter is consistently affected. Another frequent affectation is that occurred during labor, because of hypoxia-ischemia problems. In this case, the affectations of the brain can be very different in localization and extension.

Despite the fact that the central nervous system is able for self-repair damages for years, usually the ability of this self-repair is not large enough for achieving a normal functionality. In fact, in our study, some of the children were older than 2 years old, a period of time from which it is considered that the damage is already established and significant improvements are unlikely to appear.

Disorders of the human visual system can be divided into at least 2 categories, those that affect the anterior visual pathways and those that affect retro geniculate or posterior pathways (optic radiations and visual cortex).[25] The term "amaurosis" is referred to the vision loss or weakness that occurs due to an extraocular cause, at both retro geniculate and anterior visual pathways, including the optic nerves. Traumatic or ischemic lesions in the primary visual cortex result in

varying loss of vision; depending on the size and location of these defects, the visual field can be affected by scotomas, hemianopsia, or a complete loss of vision.[26] Several terms were used in the literature for the blindness due to occipital cortex damage, like "cortical blindness" or "cortical visual impairment" (CVI). Although "CVI" is preferred,[27] because "blindness" implies total loss of vision and there is often some recovery degree of visual function after the lesion occurred, this term is unfortunately equally misleading in describing many visual impairment resulting from primarily deep subcortical white matter insults (periventricular leukomalacia).

It is thought that brain injury involving the striate cortex has a better prognosis than those injuries that involve the optic radiations, like periventricular leukomalacia, because the injury is more focal.[27, 28] The prognosis is better for children below the age of three years but most are expected to remain visually handicapped and unable to function normally.[29] In this sense, it was reported a significantly better outcome in patients under the age of 40 without other impairments and there was limited or no chance of recovery in patients with bilateral occipital lesions caused by a stroke.[30] In addition, visual recovery is seen more often in those cases involving children than in the cases involving adults,[27] and after 3 months post-lesion spontaneous recovery was very seldom.[30, 31]

Several results of studies using animal and human models have indicated a remarkable capacity for functional reorganization of preserved cell populations in the striate cortex.[32] In humans, visual stimulation programs improve the visual rehabilitation in patients with CVI and any improvement in individual not receiving visual stimulation could be due to spontaneous and random visual stimulation in the environment.[33]

It has been shown that training, sensory input and brain lesions can modify cortical representation areas and subcortical structures.[34-38] Focal brain lesions lead to extensive neurophysiologic and anatomic changes in the peri-infarct region, in other areas in the injured and intact hemispheres as well as in subcortical structures, in a complex, lesion, and time-related way. Specific aim-related training can influence the process, and the training effect can be enhanced by neurophysiologic and pharmacologic manipulations.[39, 40]

Regeneration can be considered the optimal example of plasticity in the central nervous system.[41] Particularly important regarding adult neurogenesis were the discoveries of self-renewing cells with multilineage potential in the adult mammalian brain,[42,43] the human brain included.[44,45] There are two sites with a high density of proliferating progenitor cells in the adult brain: the sub granular zone (SGZ) of the dentate gyrus of the hippocampus and the subventricular zone (SVZ). These regions maintain the neurogenic potential in a subset of radial glial fibrillary acidic protein (GFAP) positive astrocytes.[46,47] It has been shown that striate, neocortex,[48] cortex,[49] or hypothalamus,[50] could be neurogenic active sites too. In addition, several researches showed that neurogenesis is improved in dentate gyrus (DG) and SVZ in the injured brain, at both in diffuse and in focal ischemic lesions.[51-52] Even, in experimental animal models, it has been shown that intraventricular infusion of Epidermal Growth Factor (EGF) and Erythropoietin, but none of them alone, has been reported to induce new cortical tissue including neurons after small frontal cortical devascularization lesions in rats.[53]

We utilized a tachistoscope as a stimulation method of both visual hemifields and we intended to maximize the cell activating effect in the striate cortex of both hemispheres. According to Widdig et al.,[32] the selective activation of cells in different functional areas of the striate cortex should be reached by the repetitive and specific photic stimulation of areas involved in light and dark, shapes or movement.

However, it is unlikely that visual stimulation alone could be responsible for the changes observed in VEPs after the treatment. These indicate that the combined treatment led to an improvement of the neurological driving from the retina to visual cortex. GH administration had to have a significant influence for achieving this improvement.

We currently know that GH plays a very important role at the central level as a neurotrophic factor.

The growth hormone – insulin-like growth factor-1 system induces neurogenesis and increases brain plasticity.[15] GH and IGF-1 are expressed in the brain,[54, 13] and both hormones can cross the blood-brain barrier.[54,] The GH receptor (GH-R) and the IGF-1 receptor (IGF-1-R) are widely expressed in several zones of rodent and human brain, including the hippocampus.[55] Particularly, GH, GH-R and IGF-1-R are expressed in hippocampal neural progenitors, acting on the proliferation and differentiation of these neural stem cells.[56,13] Thus, besides its major role in several metabolic processes, the GH – IGF-1 axis has multiple and important neurotrophic effects, related to cell proliferation and survival, both in the central and

peripheral nervous system.[13] According to this, GH-R expression is increased in the subventricular zone after focal ischemia,[57] and GH has been demonstrated to increase cell proliferation in the brain of adult hypophysectomized rats.[58] Similarly, IGF-1 increases cell proliferation in hippocampal cells,[56, 58] and its expression is increased in the affected brain hemisphere after an ischemic injury.[60,61]

A recent study describe that plasma levels of GH/IGF-I influence glial turnover in the white matter.[62] It is not clear whether the maintenance of Oligodendrocyte Precursor Cells (OPCs) and oligodendrocyte turnover in the adult brain serves normal function or only provides a rapidly recruitable population of cells for myelin repair following damage. Proliferation of oligodendrocyte precursors and recruitment of new, myelinating oligodendrocytes from immature precursors contribute to myelin repair following demyelinating lesions. Following demyelination, proliferation of OPCs and commitment, differentiation and survival of adult-born oligodendrocytes all appear to be targets of regulation by inflammatory cytokines and growth factors.

The GH/IGF-I system appears to play a particularly critical role in myelin repair. IGF-I expression is induced in multiple models of demyelination and is increased during remyelination.[63-65] Treatment with IGF-I or overexpression of IGF-I in transgenic mice inhibits oligodendrocyte death during demyelination and/or enhances remyelination following demyelinating lesions.[66-68] Studies of lysolecithin-induced demyelination in the spinal cord of young adult and old adult rats suggest that slower and less effective increases in IGF-I expression contribute to an aging-related decrease in the efficacy of remyelination,[69] which appears to be attributable to impairments in both OPC recruitment and differentiation of newborn oligodendrocytes.[70, 71]

IGF-I expression is induced by GH,[72] thus GH-deficient children show low plasma values of IGF-I and normal values are recovered after GH replacement. The possibility exists that remyelination observed in our study, as showed by the improvements in VEPs latencies, might be due to increased plasma IGF-I values. This does not exclude a direct effect of GH on myelination. In fact, our group was the first to describe how GH administration induced sciatic nerve repair after transection in rats by increasing Schwann cell proliferation and myelin formation.[73] In addition, GH induces EGF and EGF-R expression, factors recently involved on central nervous system remyelination.

Very interesting is the fact that GH treatment was able for inducing full regeneration in a very injured brain in one child in our study. To our knowledge this is the first time that such an effect has been described in humans. This agrees with the studies in which GH has been demonstrated to be a pivotal factor playing a key role in neurogenesis and with our recent data in children with cerebral palsy showing significant motor and cognitive improvements after GH treatment administered together with physical and cognitive rehabilitation.[21,22]

In all, our data show that GH administration together with visual stimulation is a useful tool for repairing injuries in the visual pathway, particularly those associated to demyelination or lack of myelination. Despite that we studied children with cerebral palsy and we did not analyze whether any or all of them suffered GH-deficiency it is likely that the hormone may also play a regenerative role in patients with normal GH secretion.

Conclusions

Growth hormone administration together with specific visual stimulation plays a key role in the repair of the visual pathway in children with cerebral palsy from different ethiologies. The treatment is safe and clinical positive results can be seen in a short period of time when the age of the children is below 3 years old.

Conflicts of Interest Statement

The authors have no conflicts of interest to declare.

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